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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,776	06/21/2002	Kei Tashiro	29288.5600	2614

20322 7590 02/23/2006

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EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 02/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,776	TASHIRO ET AL.	
	Examiner	Art Unit	
	Shafiqul Haq	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/24/06 has been entered.
2. Claim 8 has been cancelled.
3. Claims 1-7 and 9-16 are pending and under active prosecution.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-7 and 9-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
6. Steps (d) and (e) appear to describe components of a composition but should be written as method steps. For example, step (d) may be written as "adding a conjugate including -------" and step (e) may be written as "adding a lanthanoid metal ion to bind the conjugate of (d), the composite being ----------.
7. With respect to claim 4, chemical formula of the fluorescent structural portion is spelled incorrectly. Appropriate correction is required.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-7 and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of 1) Yuan et al (Anal. Chem. 1998, Vol. 70, No.3, pp. 596-601) or Matsumoto et al (US 5,859,297) and in view of 2) Pennanen et al (Int. J. Immunopharmacol. 1995, Vol. 17, No. 6, pp. 475-480).

The claims of the present application recite a time-resolved fluorescent immunoassay method for detection of cytokine in biological sample using a streptavidin (or avidin)-lanthanide metal ions conjugate.

Yuan et al disclose a time resolved immunoassay method for detection of alpha-fetoprotein in biological sample (serum) (see title and abstract) comprising the following: (a) anti AFP antibody (first antibody) including a portion bound to a solid-phase and a region bindable to AFP; (b) the AFP; (c) a second antibody including a region bindable to the AFP and a portion to which biotin is bound; and (d) a conjugate including streptovidin (SA) and a fluorescent structure portion (BHHCT) capable to being complexed with a lanthanide metal ion (Eu+3) (see page 597, fig 1 and page 598, fig.2). The fluorescent structure portion of fig.1 (BHHT and BHHCT) anticipate formula (I) and (III) of the present application. Fluorescence is measured after composite is formed on the solid phase and both solid phase measurement and after dissolution measurement are disclosed (page 598, fig.2).

Matsumoto et al. also disclosed time resolved immunoassay method for detection (both solid phase and liquid phase measurement) of alpha-fetoprotein in a sample (see abstract and column 24, lines 15-20). The fluorescent structural portion of formulas (I), (II) and (III) of claims 1, 3 and 4 of the present inventions are disclosed in this reference (see abstract; column 2, formula (1), (2) and (3); column 19, compound (j') and (j)) that are labeled with avidin or streptavidin (column 15, lines 55-62; column 20, lines 63-67) and complexed with lanthanide metal ions (column 5, lines 35-37 and column 25, lines 15-20). The time-resolved fluoroimmunoassy for detection of AFP includes first antibody (anti-human AFP)(column 23, line 29), human AFP (column 23, line 45), a biotinylated second antibody (biotinylated goat anti-rabbit antibody) (column 23, lines 57-58) and a streptavidin-(fluorescent structural portion)-Eu^{+3} complex (SA-BHHCT-Eu^{+3}) (column 23, lines 65-66).

Both Yaun et al and Matsumoto et al. disclose that use of β-diketone ligand (BHHCT) improves detection sensitivity. Yaun et al. discloses that use of β-diketone ligand (BHHCT) gave remarkable superiority over conventional organic fluorescent labels and other lanthanide labels in time resolved fluorometric determination of AFP as the detection limits are greatly improved (page 597) and Matsumoto et al. also disclose that the use of SA-BHHCT-Eu^{3+} in a time-resolved immunoassay, remarkably improved the detection limit of AFP (from 1ng/ml to 10^{-6}ng/ml; column 24, lines 15-25). Therefore, incorporation of β-diketone fluorescent structure portion

(BHHCT) is desirable for detection of low level analytes by time-resolved immunoassay.

Although Yuan et al and Matsumoto et al. disclose detection of alpha-fetoprotein in biological sample employing streptavidin-(fluorescent structural portion)-lanthanide complex (e.g. SA-BHHCT-Eu^{+3}) in time-resolved fluoroimmunoassay, but they fail to disclose detection of cytokine in biological fluids as claimed in the present applicaiton.

Pennanen et al disclose detection of cytokine in a sample by time-resolved fluoroimmunoassay comprising primary antibody (first antibody) bound to solid phase (e.g. microtiter strips), biotinylated second antibody and europium labeled streptavidin (see title and page 476, right column, lines 13-48). Pennanen et al. refer to cytokines and other cytokines (page 479, line 5 of 1st paragraph, right column) and do not exclude chemokines (i.e chemotactic cytokines).

Since, detection of cytokine by time-resolved fluoroimmunoassy using lanthanide-streptavidin complex is common and know in the art (Pennanen et al) and use of β-diketone ligand (BHHCT) is desirable in time-resolved fluoroimmunoassay as it greatly improves detection sensitivity (Yuan et al or Matsumoto et al), it would have been obvious at the time of the invention to a person of ordinary skill in the art to include cytokine as an equivalent analyte for detection in the method of Yuan et al or Matsumoto et al, with the expectation of detecting/measuring of cytokine with a high sensitivity in a sample with a reasonable expectation of success. Since it is known that cytokines are present in biological

samples in low concentration, one would be motivated to use the techniques of the primary references to enhance the fluorescence detection of the low level analyte.

The features of the dependent claims are either specifically described by the references (e.g. for microtiter plate of claim 15, see page 598, lines 49-55, left column and for the "dilution of biological fluid sample" of claim 2, see Yuan et al, right column, lines 8-13) or constitute obvious variations in parameters which are routinely modified in the art (e.g. heat treatment of sample to expose epitopes).

10. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yuan et al or Matsumoto et al as described above in paragraph 6 and further in view of Wagner et al. (US4,680,275).

The above references in paragraph 6, disclose a time-resolved fluorescent immunoassay method for detection of cytokine in biological sample using a streptavidin (or avidin)-lanthanide metal ions conjugate but, fail to disclose different components in a kit format.

Wagner et al. disclose time-resolved Fluorescence immunoassay method utilizing lanthanide ion such as europium or terbium chelated with organic ligand such as beta-diketone for sensitive detection of analyte in a sample. The invention also provides a reagent kit or package of materials for accomplishing an assay for an analyte in accordance with the method of the invention.

Since, packaging of immunoassay components as a kit format is common and well known in the art (Wagner et al), it would have been obvious at the time of the invention to a person of ordinary skill in the art to provide Yuan et al or Matsumoto et

al with components of the immunoassy as a kit format for ease and convenience in assay performance.

Response to Argument

11. Applicant's arguments and amendments filed 11/29/2005 have been fully considered but are not persuasive to overcome the rejections under 35 USC 103.

While applicants state chemokines are present in very low levels in biological fluids, applicants have not set forth any adequate reasoning as to why chemokines would not be expected to be equivalent analytes as established by the examiner i.e. there appears to be no reason to expect that a chemokine would not bind with its corresponding antibody on a solid support. Use of Beta-diketone ligand (BHHCT) as a direct label gives remarkably high sensitivity with low detection limit and the motivation for using beta-diketone ligand (BHHCT) in primary references have been discussed in paragraph 6 of this office action. Applicants have not adequately addressed as to why it would not be obvious to substitute one known analyte for another equivalent analyte in the method of primary references while primary references have motivation and teaching for sensitive detection of an analyte. If chemokines were present in serum at high levels, it is reasonable that one would not seek for a high sensitive method of detection but, since it is known that cytokines are present in biological samples in low concentration, one would obviously be motivated to use the techniques of the primary references (that teach high sensitive detection) to enhance the fluorescence detection of the low level analyte.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHAFIQUL HAQ
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